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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
03/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,459	BARNEA ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-1-37, 41, 42, 50-71* is/are pending in the application.

4a) Of the above claim(s) *1-36,41,42 and 50-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The present application was filed containing a power of attorney to Sol Sheinbein, D'vorah Graeser, Rochel Aboudi and Martin Moynihan. A correspondence address was supplied for G.E. Ehrlich (1995) Ltd c/o Mr. Anthony Castorina. No address was supplied for Sol Sheinbein, D'vorah Graeser, Rochel Aboudi and Martin Moynihan except through G.E. Ehrlich c/o Mr. Castorina.

Mr. Sol Sheinbein was excluded from practice before the Patent and Trademark Office (Office). The Office does not communicate with attorneys or agents who have been suspended or excluded from practice.

As a correspondence address, other than to G. E. Ehrlich c/o Mr. Anthony Castorina, is not of record, this Office action is being mailed to the other practitioners of record at his/her last known address as listed on the register of patent attorneys and agents. To ensure that a copy of this Office action is received in a timely manner to allow for a timely reply, a copy of the Office action is being mailed directly to the address of the inventor first named in the declaration or oath. Any reply by Applicant(s) should be by way of the remaining practitioner(s) of record and should include a new correspondence address.

2. Applicant's response filed 12/13/07 is acknowledged and has been entered.

3. The terminal disclaimer filed on 7/6/07 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,867,283 has been reviewed and is accepted. The terminal disclaimer has been recorded. Applicant's said terminal disclaimer has overcome the obviousness-type double patenting rejection of record.

4. Claim 37 is presently being examined.

5. Applicant is reminded that the disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 27 at line 18 and on page 51 at line 22. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP 608.01.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 37 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 37 was rejected in the last Office Action mailed 2/23/07 on the same basis as enunciated herein. Applicant's cancellation of claims 38, 39 and 43-49 has necessitated the following new rejection.

The specification does not disclose how to use the instant invention, a peptide that is SEQ ID NO: 20.

The specification has not enabled the breadth of the claimed invention because the claim encompasses: a peptide that is SEQ ID NO: 20, a peptide that may not be immunogenic *in vitro* or *in vivo*, including in the latter instance for treatment, and which may not be a marker for ovarian cancer. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the recited peptide can produce a therapeutic endpoint. The specification discloses no working examples with regards to the in vivo administration of the said peptide, nor that the peptide is capable of stimulating CTL *in vitro*. The discloses use of the peptide or of a pharmaceutical composition comprising SEQ ID NO: 20 is to treat cancer, either by in vitro stimulation of CTL for adoptive therapy or in vivo administration, respectively (page 27 at liens 4-6, Tables 8 and 9, page 114 at lines 19-30), or to study the peptide for its significance as a cancer antigen (page 54 at lines 22-25).

The specification discloses that peptide SEQ ID NO: 20 was detected on ovarian cancer cell line UCI-107, that it is a subsequence of testis-cancer antigen MAGE-B2 tumor-associated antigen and that a synthetic version of the said peptide can reconstitute HLA-A2 on the surface of RMA-S-HHD cells ([1276] and [0050]). However, the specification also discloses that peptide SEQ ID NO: 20 was not detected on a second ovarian cancer cell line UCI-101 (Table 9 spanning pages 58-59). The specification does not disclose that SEQ ID NO: 20 is capable of stimulating CTL *in vitro* or of inducing an immune response *in vivo*. The specification discloses that "Once tumor specific MHC bound peptides are identified and their ability to stimulate an immune response is demonstrated, such peptides become candidates for adoptive immunotherapy…The potential usefulness of identified immunogenic peptides should be evaluated by the presence of specific T cells directed against them in patients inflicted with the particular cancer using standard assays such as ELISPOT and CTL. The assay of immunizing mice with the peptides described herein was meant to serve first as validation that these peptides are indeed MHC bound peptides with affinity for the HLA-A2.1 and as the preliminary indication of their immunogenic potential" (page 114 at lines 19-30).

Evidentiary reference Chaux *et al* (J. Immunol. 1999, 163: 2928-2936, of record) teach varying results between peptides used *in vivo* in different clinical trials, injection of a HLA-A1 binding MAGE-A3 peptide correlated with tumor regression in about one third of patients, dendritic cells loaded with to other HLA-A1 binding peptides yielded only a partial response in one patient, and dendritic cells pulsed with two other HLA-A2 binding peptides produced no tumor regression. Chaux *et al* teach that it is necessary to monitor CTL responses of patients to provide information on the immunogenicity of various MAGE-A1 peptide, and that the immunogenicity of the peptides may vary in different individuals (especially Discussion section).

Evidentiary reference Marchand *et al* (Int. J. Cancer 80: 219-230, 1999, of record) teach "Considerable further progress is needed, however, before immunization with tumor-specific antigens recognized by T cells becomes an effective and generally applicable cancer therapy" (second to last sentence of article).

Evidentiary reference Bodey *et al* (Anticancer Research 20: 2665-2676, 2000, of record) teach "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy (page 2665 at column 2). Bodey *et al* further teach "the use of active specific immunotherapy for cancer is still in its infancy despite several decades of clinical and basic research" (page 2668 at column 2).

Evidentiary reference Gao *et al* (J. Immunother. 23: 643-653, 2000, of record) found that although anti-tumor CTL response was enhanced by immunization, the tumors failed to regress due to an association with lack of CTL migration to the tumor sites (abstract). Thus, Gao *et al* teach that activation of peptide epitope-specific CTL is not an appropriate endpoint, and an estimation of efficacy based upon this factor is not predictive of actual efficacy of treatment *in vivo*.

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Ther. 1(3): 497-510, 2001, of record) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine" (last paragraph at column 2 on page 505).

Evidentiary reference Berger *et al* (Int. J. Cancer. 111: 229-237, 2004, of record) teach "Since strong CTL responses as observed in this patient are the goal of cancer vaccination but are so far only rarely observed, the thorough analysis of patients exhibiting either exceptional clinical and/or immunologic response appears critical to understanding how vaccine therapies work and can be further improved." (abstract). Berger *et al* further teach "immune therapy for tumor patients aims at harnessing the immune system to fight cancer. Indeed, clinical trials have already shown that tumor-

specific T cells can be induced even in advanced cancer patients. The induction of tumor-specific T cells, however, is not necessarily associated with a clinical response. A major obstacle in evaluating the success of a cell-based immunotherapy lies in the fact that systemic immune responses detected in the blood may not reflect the actual situation in the tumor." (column 1, page 229). Berger *et al* teach "…tumor-reactive T-cell clones persisted for prolonged time in circulation but failed to infiltrate the analyzed tumor lesions. A possible explanation for this discrepancy is provided by the recent report from a transgenic mouse model that tumors may develop an intrinisic resistance to leukocyte infiltration and effector function that prevents even persistently high levels of activated tumor-specific T lymphocytes from eradicating the tumor" (paragraph spanning columns 1-2 on page 236).

Evidentiary reference Celis (J. Clin. Invest. 2002, 110(12: 1765-1768, of record) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating CTL responses, either because of their rapid biodegradation (e.g., by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Thus, even ***if*** there were factual evidence that patients with ovarian cancer or any other cancer or pathological condition could produce a peptide-specific immune response to the SEQ ID NO: 20 peptide, there is no factual evidence that the patient's condition would clinically improve, *i.e.,* be 'treated'. Based upon the teachings of the evidentiary references cited herein, it is evident that eliciting an immune response is not sufficient to evoke a clinically significant or specific anti-tumor effect. In addition, the presence of peptide SEQ ID NO: 20 on one ovarian cancer cell line, but not another, does not establish the peptide as an ovarian cancer marker.

Since SEQ ID NO: 20 has not been demonstrated to be immunogenic, it is unpredictable whether at least one modification such as recited in claims 46 and 47 could render the peptide more immunogenic and be used for the disclosed purpose.

Therefore, because of the demonstrated unpredictability in the art of cancer immunotherapy, in the absence of sufficient exemplification and guidance, one skilled in the art cannot make and/or use the pharmaceutical composition comprising the peptide with a reasonable expectation of success. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

8. SEQ ID NO: 20 appears to be free of the prior art.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Group 1640, Technology Center 1600
March 3, 2008

/GRE/
Primary Examiner, Art Unit 1644